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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,697	09/17/2001	Anne-Francoise Burnol	045636-5051	8953

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,697	BURNOL ET AL.	
	Examin r	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *8, 10, and 12* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Response and Amendment filed 24 November 2003 has been received and entered in full. Claims 1-7, 9, 11, and 13-20 have been cancelled. Claims 8, 10, and 12 have been amended.

2. Concerning Applicant's request for review of all figures by the Official Draftsman, it is not granted. Figures are currently reviewed by done by the Office of Initial Patent Examination (OIPE) and the Examiner; an PTO-948 is no longer required [MPEP §608.02 and §608.02(e)].

3. The Declaration under 37 C.F.R. §1.132 by Anne-Françoise Burnol filed on 24 November 2003 has been received and taken into consideration.

4. It is noted that the Examiner did not include claims 8-9 in the rejection as set forth in the previous Office Action (23 May 2003). Therefore, regardless of the amendments made, the Examiner has not made this second Office Action final.

Withdrawn Objections And/Or Rejections

5. The Objection to the Drawings as set forth at pp. 3 ¶4 in the previous Office Action (23 May 2003) is hereby *withdrawn* in view of Applicant's submission of replacement Drawings (24 November 2003).

6. The Objection to claim 9 as set forth at pp. 3 ¶5 in the previous Office Action (23 May 2003) is hereby *moot* in view of Applicant's cancellation of said claim (24 November 2003).

7. The Rejections of claims 9, 11, and 13 as set forth in the previous Office Action (23 May 2003) are hereby *moot* in view of Applicant's cancellation of said claims (24 November 2003).

8. The Rejection of claims 8, 10, and 12 under 35 U.S.C. §112 ¶1 as set forth at pp. 3-6 ¶6-14 in the previous Office Action (23 May 2003) is hereby *withdrawn in part* in view of Applicant's amendments (24 November 2003).

9. The Rejection of claim 10 under 35 U.S.C. §103(a) as set forth at pp. 6-8 ¶15-22 in the previous Office Action (23 May 2003) is hereby *withdrawn* in view of Applicant's amendments (24 November 2003) and the Declaration under 37 C.F.R. §1.132 by Anne-Françoise Burnol filed on 24 November 2003.

Objections And/Or Rejections

Specification

10. The disclosure is objected to because of the following informalities: the Specification does not include a section entitled "Brief Description of the Drawings". The Examiner notes that the figures are described but the subheading is lacking. Applicant may obviate this Objection by inserting said subheading into the Specification (pp. 10 line 35). Appropriate correction is required.

Sequence Rules

11. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein. The Specification does not include the appropriate SEQ ID NO's for

the sequences listed in Figure 2. The Examiner notes that the Applicant may correct this by inserting the appropriate SEQ ID NO's (pp. 11 line 11). Correction is required.

Claim Objections

12. Claim **12** is objected to because of the following informalities: the use of Arabic numerals for the subheadings in claim 12 may be confused with additional claim numbers. To avoid such confusion the Examiner respectfully suggests that Applicant amend said claim to use letters as in Claim 10 for the subheadings. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. The rejection of claims **8, 10,** and **12** as rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *the fragment of the PIR domain wherein said fragment consists of SEQ ID NO: 5 or SEQ ID NO: 6 and the method as claimed in claims 10 and 11 wherein the fragment consists of SEQ ID NO: 5 or 6*, does not reasonably provide enablement for *variants, mutations, truncations, alterations, and isoforms of SEQ ID NO: 5 and 6* is maintained *in part*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate

in scope with these claims for the reasons as set forth at pp. 3-6 ¶6-14 in the previous Office Action (23 May 2003) and herein.

14. Applicant traverses the rejection of remaining claims 8, 10, and 12 on the following grounds: **(a)** claims 11 and 13 have been cancelled and **(b)** claims 10 and 12 have been limited to in vitro methods by way of amendment.

15. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons. The rejection as it pertained to claims 11 and 13 is *moot* in view of Applicant's cancellation of said claims. The method of claims 10 and 12 now reads as limited to *in vitro* use, which the Examiner acknowledges as enabled.

16. However, the claims are drawn very broadly to any fragment of hGrb14's PIR domain which includes positions 365-407 or 353-436 as well as methods of using said fragments in *in vitro* screening assays. The language of said claims encompasses variants, derivatives, substitutions, mutants, and as of yet unspecified fragments.

17. The specification teaches that SEQ ID NO: 5 and SEQ ID NO: 6 encode the PIR domain of hGrb14 and can be used in *in vitro* screening assays.

18. The specification fails to provide any guidance for the successful isolation, characterization, and use of any other fragments of hGrb14, and since resolution of the various complications in regards to predicting the activity of a fragment of a protein is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations

with known related activity of SEQ ID NO: 5 and 6 to correlate with any number of fragments, mutants, and variants. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

19. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a given fragment based solely on its performance of 2 examples (SEQ ID NO: 5 and 6) as highly problematic (see MPEP §2164.01). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in screening assays, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

20. The following references are cited herein to illustrate the state of the art of protein biochemistry.

21. Regarding derivatives and fragments of hGrb14 due to the language "corresponding to", which includes any protein with is similar in structure or nature to hGrb14, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural

determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues;

therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

22. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from prophetic consideration to the isolation, characterization, and use of the undisclosed hGrb4 fragments as exemplified in the references herein.

23. Claims **8, 10,** and **12** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "corresponding" in claims 8, 10, and 12 is a relative term which renders the claim indefinite. The term "corresponding" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The American Heritage® Dictionary of the English Language (Fourth Edition 2000 by Houghton Mifflin Company) defines "corresponding" as similar to in nature or structure thus it is read as "open claim language" and hence renders the exact nature of the transitional phrase in said claims unclear. Further it is unclear whether or not the claim encompasses sequences with substitutions in the recited region such that the metes and bounds of the claimed invention cannot be determined. The Examiner respectfully suggests the use of "comprising" or "consisting of" for transitional phrases (see MPEP §2111.03).

24. Claims **8, 10,** and **12** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims include parenthetical matter which renders the claims indefinite. It is not clear to the skilled artisan whether SEQ ID NO: 5 and SEQ ID NO: 6 per se are claimed or specific positions of hGrb14 or even any protein which contains the identical stretch of amino acids.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

25. Claim **8** is rejected under 35 U.S.C. 102(b) as being anticipated by Daly *et al.* (24 May 1996) "Cloning and Characterization of *GRB14*, a Novel Member of the *GRB7* Gene Family." The Journal of Biological Chemistry **271**(21): 12502-12510 (**IDS**).

26. As currently presented, claim 8 requires a fragment of the PIR domain of hGrb14 wherein said fragment encompasses amino acid positions 365-407 (as shown in SEQ ID NO: 5) and a fragment encompassing amino acid positions 353-436 (as shown in SEQ ID NO: 6).

27. Daly *et al.* teaches the cDNA and amino acid sequence of GRB14 which includes the amino acid stretch that shares 100% sequence homology to both SEQ ID NO: 5 and SEQ ID NO: 6 (Figure 2). Daly *et al.* also teaches that the sequence shown in Figure 2 is derived from a human cDNA library and is Grb14, while the notation is not identical to the application, "h" preceding a gene name is defined in the art as referring to "human" (Daly *et al.* Table I and the instant Specification at Figure 2 & 3). While not teaching that the sequence in Figure 2 contains a "PIR domain" *per se* it has been established that a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore since the sequence as taught by Daly *et al.* shares 100% homology with both SEQ ID NO: 5 and SEQ ID NO: 6, their properties are inherent and therefore the same thus meeting the limitations of claim 8.

Summary

28. Claims **8, 10,** and **12** are hereby rejected.

29. The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

a. US 6,465,623 B2 (15 October 2002) Daly & Sutherland

b. US 2003/0044834 A1 (6 March 2003) Daly & Sutherland

c. US 2003/0129639 A1 (10 July 2003) Daly & Sutherland

d. WO 96/34951 (7 November 1996) Daly & Sutherland

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
January 16, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER